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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,484	07/21/2005	Yoshihisa Nishibe	26430U	5312

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EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
08/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,484	NISHIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Remarks filed 13 May 2010. The Examiner acknowledges the following:

No claims have been amended, added or canceled. As such, the claim contains no new matter.

Thus, claim 1 still represents all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS), have been submitted for consideration.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 27 November 2009 since the art which was previously cited continues to read on the instantly claimed invention.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Karlsson et al. (U.S. Patent Publication 2002/0065256) in view of the Material Safety Data Sheet (MSDS) for Metolose 60SH.

Karlsson et al. teaches the ciclesonide and HPMC suspension, as described above. Said teachings from the withdrawn rejection under 35 USC 102(b) are reproduced here for Applicants' convenience:

The composition is taught by Karlsson et al. at claims 7, 9, and 10. Claim 10 teaches a thickening agent which is further defined as including hydroxypropyl methylcellulose (see [0040] and [0041]).

However, Karlsson does not teach the specific grade of HPMC (HPMC 2910) as cited in claim 3. Per Applicants' specification, the claimed HPMC 2910 is also known industrially as Metolose 60SH. Shin-Etsu Co. produces the HPMC of the present invention and provides an MSDS which further provides a Recommended Use for Metolose 60SH as a thickening agent.

Since the ingredient of the composition is the chemically the same, it follows that particular grade of HPMC used is a result-effective parameter that a person having ordinary skill

in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to employ the optimal grade hydroxypropyl methylcellulose within the composition in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of this ingredient would have been obvious at the time of Applicant's invention.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Karlsson et al. and Nagano et al. (WO 01/28563 A1).

The instantly amended claim 1 is directed to an aqueous suspension comprising ciclesonide and hydroxypropylmethylcellulose 2910 which is sterilized via autoclaving and wherein the resulting preparation comprises at least 95% ciclesonide. Per MPEP §2113, product-by-process limitations hold no patentable weight. Thus, regardless of how the instantly claimed ciclesonide-containing aqueous suspension is made sterile, the fact still remains that a sterile ciclesonide-containing aqueous suspension results.

The teachings to Karlsson et al. are discussed above. Again, Karlsson does not expressly teach using HPMC 2910.

The invention practiced by Nagano et al. is directed to an aqueous pharmaceutical composition containing ciclesonide and HPMC, wherein the ciclesonide is dispersed (e.g. suspended in an aqueous medium in the form of solid particles (Abstract). Compositions 1-5 of Example 1, expressly teach aqueous formulations comprising both ciclesonide and HPMC 2910. Ciclesonide concentration of the preparations was evaluated as being 100% (pg. 7, lines 26-34).

It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to have added HPMC 2910 to the invention of Karlsson et al. as a form of HPMC to be mixed and sterilized with ciclesonide. As discussed before, absent any evidence to the contrary (i.e. physical or chemical differences between HPMC 2910 and HPMC), the ordinarily skilled artisan would have been motivated to substitute one compound for the other and would have still had a high expectation of successfully arriving at the instantly claimed invention.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claim 1 under 35 USC 103(a) as being unpatentable over Karlsson et al. in view of the Material Safety Data Sheet (MSDS) for Metolose 60SH, as well as being unpatentable over Karlsson et al. in view of Nagano et al., have both been fully considered, but neither is persuasive.

Applicants continue to argue that Karlsson teaches away from the instant composition on the grounds that the reference at ¶[0009] teaches that terminal sterilization of aqueous suspensions of glucocorticosteroids have all proved "unsatisfactory" and that moist heat sterilization leads to "unacceptable" results. Applicants also revisit the limitations of the claim: "An autoclaved sterile aqueous suspension comprising ciclesonide and [HPMC], wherein the concentration of the ciclesonide after it is autoclaved is 95% or more compared to that before it is autoclaved."

In response, the Examiner respectfully finds Applicants' remarks unpersuasive particularly since the reference clearly teaches that glucocorticosteroid aqueous suspensions have

been sterilized via autoclave. As to both the "unsatisfactory" or "unacceptable" results acquired due to autoclaving, the reference is completely silent to any discussion which would suggest a diminished product concentration (i.e., less than 95%). The only negative result reported by Karlsson is a change in particle size. Applicants' instant composition comprises a concentration (e.g., an amount) of ciclesonide which is 95% or more. The "wherein" clause (MPEP §2111.04) merely recites that the same concentration of active is present prior to and after the aqueous suspension is autoclaved. Thus, while there are some negative results from treating the suspension in such a manner, Applicants have failed to show how this teaching (e.g., "an unacceptable change in particle size" ¶[0009]) necessarily diverges from the instantly claimed invention or in any way relates to the amount of ciclesonide in the composition.

Lastly, concerning Applicants' traversal of the obviousness rejection over Karlsson and Nagano, the Examiner respectfully maintains that while the Karlsson reference expressly teaches autoclaving of aqueous glucocorticoid suspensions, it discusses different drugs (e.g., ciclesonide) and excipients (e.g., HPMC) as being a part of the formulation. The Nagano reference is relied upon to demonstrate that the specific combination of ciclesonide and HPMC is known in the art. In response to Applicants' remark alleging that the Nagano reference is completely silent regarding sterilized products, the Examiner respectfully points out that the Nagano reference expressly discloses the production of pharmaceutical compositions. That is, the reference teaches compositions to be applied to into or onto the human body. Such applications would convey to the artisan of ordinary skill that these compositions necessarily carry with them a degree of sterility or at the very least, are prepared under sterile conditions (MPEP §2123).

For these reasons, Applicants' arguments are found unpersuasive. Said rejections are therefore **maintained**.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Nagano et al. (WO 01/28563 A) and Suzuki et al. (JP 2001-048807; English Machine translation) and in further view of the Wikipedia entry for difluprednate.

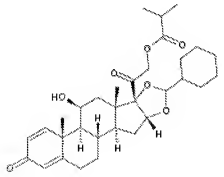
The limitations of claim 1 are discussed above.

Nagano expressly discloses an aqueous pharmaceutical composition comprising ciclesonide and HPMC, specifically HPMC 2910, wherein the ciclesonide is dispersed in an aqueous medium in the form of solid particles. Nagano further teaches that HPMC 2910 not only avoids the variations in the concentration of ciclesonide but may also function as a stabilizing component (Abstract, pg. 4, lines 31-35). The teachings of Nagano do not expressly discuss sterilizing the instantly claimed composition. However, Suzuki remedies this deficiency.

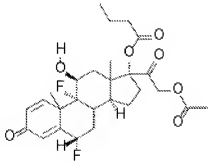
The teachings of Suzuki et al. are directed to preparing an aqueous formulation by dispersing an acetyl-based active ingredient and an additional ingredient such as a water-soluble

polymer (e.g. HPMC) (see claims 1, 2 and 4). Acetyl-based active ingredients which are taught as being available include corticosteroids such as difluprednate and budesonide. Regarding the means for achieving sterility, paragraph [0015] further teaches that the practiced formulations may undergo heat sterilization processing such as the pressurization of heat sterilization (e.g. autoclaving). Thus, it follows that drugs having acetyl substitutions such as difluprednate, and which are mixed with water-soluble polymers such as HPMC, demonstrate the ability to withstand sterilization processes which employ high heat and pressure, such as autoclaving.

Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time invention was made to have prepared an aqueous suspension of ciclesonide and HPMC and sterilize it via autoclaving. The ordinarily skilled artisan would have been motivated to combine HPMC with a drug such as ciclesonide, particularly in view of the teachings of Suzuki, which clearly demonstrates the ability of a water-soluble polymer such as HPMC to stabilize ciclesonide through its stabilization of difluprednate. Both corticosteroid compounds share very similar core ring structures, including bonding two acetyl groups bound at the same point on the 5-membered ring of the structure, as shown below:



Ciclesonide



Difluprednate

Given the ability for difluprednate to be stabilized as discussed above, it stands to reason that the ordinarily skilled artisan would be highly motivated to admix and sterilize an homologous compound such as ciclesonide and arrive at a similar result: a stable sterilized suspension.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claim 1 under 35 USC 103(a) as being unpatentable over the combined teachings of Nagano et al. and Suzuki et al. have been fully considered but they are not persuasive.

As an initial matter, Applicants' remarks directed to Karlsson are disregarded as the reference was not used in this rejection. The first and second paragraphs of Section III appears to be a typographical error.

Concerning the Nagano/Suzuki rejection, Applicants allege that the Suzuki reference contains no real teaching that would enable a person of ordinary skill in the art to arrive at the presently claimed autoclaved suspension. It is further asserted that the lack of working examples teaching how to sterilize any of the medicines listed in Suzuki is sufficient in overcoming the present obviousness rejection. Applicants set forth that budesonide is more structurally homologous to ciclesonide than is difluprednate, stating and showing that budesonide and ciclesonide share an additional acetal structure at the 16 and 17 positions. Despite this structural homology, Applicants state in their instant specification that it is known that acetal structures at the 16 and 17 positions may lead to chemical instability further asserting that ciclesonide rather than budesonide did not seem stable at high temperatures which is consistent with autoclaving. Applicants then conclude that the ordinarily skilled artisan would not be motivated to substitute

budesonide for ciclesonide on the grounds that the two compounds do not exhibit similar behavior under similar conditions. Additional discussion of the stability data in the Examples and Comparative Examples is provided, namely of the comparative "recovery rates" for ciclesonide versus budesonide and beclomethasone.

First, in response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Second, in response to Applicants' argument that the references fail to show certain features of Applicants' invention, it is noted that the features upon which Applicants rely (e.g., "recovery rate", "chemical stability" and uniformity of content) are not recited in the rejected claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It is respectfully submitted that Applicants' instant claim, as discussed above, recites an autoclaved aqueous suspension which comprises at least 95% ciclesonide and HPMC, both prior to and after autoclaving. However, in response to Applicants' statement about it being known in the art that acetal structures at the 16 and 17 positions *may lead to chemical instability*, it stands to reason that a person of ordinary skill in the art, in possession of the teachings of ***both*** Nagano and Suzuki, would not only be in possession of the specific combination of ciclesonide and HPMC, but also in possession of the process by which aqueous, glucocorticoid suspensions may be sterilized (e.g., autoclaving). Furthermore, given the limited number of glucocorticoids

discussed by the combined references (e.g., ciclesonide, budesonide and difluprednate), it also stands to reason that it would be well within the purview of said skilled artisan to employ routine experimentation in order ascertain which of the active ingredients demonstrated the best recovery, stability or content uniformity properties. Thus, in view of such experimentation, it follows that a showing of better formulation properties would motivate the ordinarily skilled artisan to substitute one glucocorticosteroid for another.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
Art Unit 1615